Determination and Evaluation of Solubility Parameter of Nabumetone Using Dioxane-Water System

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Abstract
Nabumetone, non-steroidal anti-inflammatory drug, is a poorly water-soluble drug and has low bioavailability on oral administration. One of the important methods to improve the solubility and bioavailability of a less water-soluble drug is by the use of cosolvents. The solubility enhancement produced by binary blends with a cosolvent (dioxane) was studied against the solubility parameter of solvent blends (δ₁) to evaluate the solubility parameter of drug (δ₂). Solubility parameter of drug (δ₂) was evaluated in blends of dioxane-water system. The results obtained were compared with the δ₂ values obtained using Molar Volume Method and Fedor's Group Substitution Method. The binary blend water-dioxane (10:90) gave maximum solubility with an experimental δ₂ value of 11.354 (Cal/cm³)⁰.⁵ that was comparable to the theoretical values of 11.354 (Cal/cm³)⁰.⁵ determined by Molar Volume Method and 10.1689 (Cal/cm³)⁰.⁵ when determined by Fedor's Group Substitution Method, which is still in good agreement with solubility measurement method.

Keywords: Fedor's group substitution method, molar volume method, nabumetone, solubility parameter

Conflict of Interest: None Declared!
INTRODUCTION:
Nabumetone, 4-(6-methoxy-2-naphthyl)-2-butanone, is one of the large series of non-steroidal anti-inflammatory, BCS class II drug[1-3]. It is official in USP[4-7]. Nabumetone is a prodrug that undergoes extensive first pass metabolism to 6-methoxy-2-naphthy lacetic acid (6-MNA), the major circulating metabolite. 6-MNA is mainly responsible for the therapeutic efficacy of nabumetone. It decreases prostaglandin synthesis via inhibition of cyclooxygenase, an enzyme involved in the arachidonic acid conversion[8]. Though the molecule is found to be effective orally, its therapeutic efficacy is hindered due to poor aqueous solubility[9]. The poor aqueous solubility and wettability of nabumetone give rise to difficulties in pharmaceutical formulations meant for oral or parenteral use, which may lead to variation in absorption and bioavailability[10,11]. Co-solvency is one of the methods to improve solubility especially in case of liquid formulations. The choice of the appropriate co-solvent is important to obtain maximum solubility of drug[12]. Evaluation of solubility parameter in different solvent blends of various polarities would provide important insight about the solubility of drug[13]. Solubility parameter (\(\delta\)) is an intrinsic physicochemical property that influences drug action, structure activity, in situ release and transport kinetics of a drug substances[14]. Literature survey revealed that solubility parameter of nabumetone is not estimated by any method till date. So the present study attempts to determine the solubility parameter of nabumetone in different blends of dioxane-water. Experimental values obtained were compared with the theoretical values obtained by molar volume method and Fedor’s group substitution method[15,16]. Dioxane and water were selected based on their Hildebrand values[17-19]. Water and dioxane exhibit extremities of polarity[20].

MATERIALS AND METHODS:
Nabumetone, obtained as gift sample from GlaxoSmithKline Pharmaceuticals Ltd. Nasik, India. 1, 4-Dioxane was purchased from Research Lab Fine Chemical Industry, Islampur, India. Double distilled water was used for experimental purpose throughout the study. All chemicals and reagents used in the study were of analytical grade and used as such. Double beam UV/Vis spectrophotometer, SICAN 2301, with spectral bandwidth of 2 nm, wavelength accuracy ±0.5 nm and a pair of 10 mm matched quartz cells was used to measure absorbance of the resulting solutions. Citizen balance, CX-100, was used for weighing of nabumetone.

Solubility measurements:
Experimental determination of solubility parameter was based upon the maximum solubility of nabumetone in cosolvent-water blends. For most of cases, 1, 4-dioxane and water were chosen as miscible solvent blends, which provides the two extremes of solubility parameters (\(\delta_1\)) 10.01 and 23.45 (Cal/cm\(^2\))\(^{0.5}\), respectively. Binary solvent system was prepared by using dioxane and water, ranging from 0% to 100% respectively, in screw capped vials. The final volume of binary solvent system was kept constant at 2 ml. A slight excess quantity of nabumetone was introduced into each vial and these were shaken for 3 h by keeping on rotary shaker at constant speed at 150 rpm followed by saturation equilibration for 72 h at room temperature (~ 25°C). Preliminary studies showed that this time was sufficient to ensure saturation equilibrium[21,22]. After equilibrium was reached, solutions were filtered through Whatman filter paper (No. 41) and analyzed after appropriate dilutions with double distilled water by UV Spectrophotometer at 262 nm (\(\lambda_{\text{max}}\)). All experimental results are expressed as the average of at least three determinations. The coefficient of variation (SD/mean*100) was within 2% among replicated samples for the solubility measurements.

Solubility parameter determination of nabumetone (\(\delta_2\)) was achieved using the solubility measurement method (experimental method) and by theoretical methods, namely, molar volume method and by Fedor’s group substitution method proposed by Fedor[23]. In solubility measurement method, the solubility parameter of nabumetone is assumed to be similar to that of the drug exhibits maximum solubility[24]. Hence, the solubility data (Table 1) obtained by the method described in preceding section was used to determine \(\delta_2\).

<table>
<thead>
<tr>
<th>Water: 1,4-Dioxane (%)</th>
<th>(\delta_1) (Cal/cm(^2))(^{0.5})</th>
<th>(\Delta \delta) ((\delta_1-\delta_2))</th>
<th>Solubility (g/ml)</th>
<th>Mole fraction solubility ((X_1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>100:0</td>
<td>23.450</td>
<td>+12.096</td>
<td>1.91E-05</td>
<td>1.51E-06</td>
</tr>
<tr>
<td>90:10</td>
<td>22.106</td>
<td>+10.752</td>
<td>5.01E-05</td>
<td>5.48E-06</td>
</tr>
<tr>
<td>80:20</td>
<td>20.762</td>
<td>+9.408</td>
<td>1.68E-04</td>
<td>2.34E-05</td>
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<tr>
<td>70:30</td>
<td>19.418</td>
<td>+8.064</td>
<td>5.09E-04</td>
<td>8.64E-05</td>
</tr>
<tr>
<td>60:40</td>
<td>18.074</td>
<td>+6.720</td>
<td>1.38E-03</td>
<td>7.24E-04</td>
</tr>
<tr>
<td>50:50</td>
<td>16.730</td>
<td>+5.376</td>
<td>3.42E-03</td>
<td>7.04E-04</td>
</tr>
<tr>
<td>40:60</td>
<td>15.386</td>
<td>+4.032</td>
<td>8.76E-03</td>
<td>2.28E-03</td>
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<tr>
<td>30:70</td>
<td>14.042</td>
<td>+2.688</td>
<td>1.18E-02</td>
<td>3.42E-03</td>
</tr>
<tr>
<td>20:80</td>
<td>12.698</td>
<td>+1.344</td>
<td>1.38E-02</td>
<td>4.40E-03</td>
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<td>10:90</td>
<td>11.354</td>
<td>0.000</td>
<td>1.76E-02</td>
<td>6.12E-03</td>
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<tr>
<td>0:100</td>
<td>10.010</td>
<td>-1.344</td>
<td>1.40E-02</td>
<td>5.26E-03</td>
</tr>
</tbody>
</table>

Table 1: Mole fraction solubility of nabumetone in binary solvent blends

\(\delta_1\) = Solubility parameter of solvent blend, \(\delta_2\) = Solubility parameter of drug in solvent blend. The binary solvent blends, \(\delta_1\) and \(\delta_1-\delta_2\) and the corresponding values of equilibrium experimental solubility and mole fraction solubility.
RESULTS AND DISCUSSION:
The solubility parameter of nabumetone was determined by molar volume method by calculating the mole fraction solubility ($X_2$) of nabumetone in solvent blends containing water and dioxane in different ratios as shown in Table 1. The mole fraction solubility was calculated by using the equation, mole fraction solubility, $X_2=\eta_2/\eta_1+\eta_2$ (1), where $\eta_1$ and $\eta_2$ are the number of moles of solvent and solute respectively. A plot of mole fraction solubility of nabumetone in the various ratios of the binary mixtures was made against $\Delta\delta$ ($\delta_1-\delta_2$), difference between solubility parameter of solvent and solute respectively. The solubility parameter of the solvent blend ($\delta_1$) in which nabumetone showed peak mole fraction solubility represents the solubility parameter of nabumetone ($\delta_2$).

Fedor’s group substitution method is based on the determination of solubility parameter of nabumetone ($\delta_2$) by using the Eqn. $\delta = (\Delta\Delta u / \Delta V)^{0.5}$ (2), in which $\Delta\Delta u$ represents the substituent fragment constant and $\Delta V$ represents the fragmental molar volume constant.

Further, the solubility parameter of nabumetone was determined by dividing the structure of nabumetone (fig. 1) into different fragments and corresponding values of cohesive energy per mole ($\Delta\Delta u$) and molar volume ($\Delta V$) for each fragment was obtained from literature survey as shown in Table 2.

<table>
<thead>
<tr>
<th>Drug Fragments</th>
<th>No. of Fragments</th>
<th>Cohesive Energy of Each Fragment (Cal/mol)</th>
<th>Total Cohesive Energy (Cal/mol)</th>
<th>Molar Volume of Each Fragment (Cm$^3$/mol)</th>
<th>Total Molar Volume (Cm$^3$/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>=CH</td>
<td>[6]</td>
<td>1030</td>
<td>6180</td>
<td>13.5</td>
<td>81</td>
</tr>
<tr>
<td>=C=</td>
<td>[4]</td>
<td>1690</td>
<td>6760</td>
<td>6.5</td>
<td>26</td>
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<tr>
<td>=O=</td>
<td>[1]</td>
<td>800</td>
<td>800</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>=CO=</td>
<td>[1]</td>
<td>4150</td>
<td>4150</td>
<td>10.8</td>
<td>10.8</td>
</tr>
<tr>
<td>=CH$_3$</td>
<td>[2]</td>
<td>1126</td>
<td>2252</td>
<td>33.5</td>
<td>67</td>
</tr>
<tr>
<td>=CH$_2$</td>
<td>[2]</td>
<td>1161</td>
<td>2362</td>
<td>16.1</td>
<td>322</td>
</tr>
<tr>
<td>Conjugation</td>
<td>[5]</td>
<td>400</td>
<td>2000</td>
<td>-2.2</td>
<td>-11</td>
</tr>
<tr>
<td>Ring Closure</td>
<td>[2]</td>
<td>250</td>
<td>500</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>10628</td>
<td>25004</td>
<td>98</td>
<td>241.8</td>
</tr>
</tbody>
</table>

$\delta_2=(25004/241.8)^{0.5}=(103.408)^{0.5}=10.1689$ (Cal/cm$^3$)$^{0.5}$

Table 2: Calculation of solubility parameter of nabumetone by fedor's group substitution method

$\delta_2=$ Solubility parameter of nabumetone, (Cal/cm$^3$)$^{0.5}$ = Unit of solubility parameter

Cohesive energy and molar volume of nabumetone was obtained by Fedor’s group substitution method, which divide the structure into different drug fragments.

Solubility of nabumetone was evaluated in solvent blends containing water: dioxane for the determination of $\delta_2$ as the varying blends of these provided a range of 10.01-23.45 (Cal/cm$^3$)$^{0.5}$ of $\delta_1$. The peak solubility of 0.0176 g/ml for nabumetone was observed in a solvent blend of water:dioxane (10:90) with $\delta_1$ of 11.354 (Cal/cm$^3$)$^{0.5}$.

Thus, the solubility parameter for nabumetone can be defined as 11.354 (Cal/cm$^3$)$^{0.5}$ as according to the solubility measurement method; $\delta_2$ is that value of $\delta_1$ at which the drug exhibits maximum solubility. Table 1 lists the solvent blends, the Hildebrand solubility parameter ($\delta_1$) of the solvent blends and the experimentally determined solubility’s (g/ml) of nabumetone.

The molar volume method was used to determine the peak mole fraction solubility of nabumetone in various solvent blends and the mole fraction solubility’s $X_2$ of nabumetone and $\Delta\delta$ are tabulated in Table 1. Peak mole fraction solubility ($X_2$) was determined to be 0.00612 in solvent blend of water:dioxane, 10:90) with $\delta_1$ value 11.354 (Cal/cm$^3$)$^{0.5}$, which is in agreement with the value obtained using solubility measurement method. A plot of $\delta_1$ and mole fraction solubility ($X_2$) (fig. 2) showed a bell shaped curve suggesting that both at lower and higher values $\delta_1$ =11.354 (Cal/cm$^3$)$^{0.5}$ the solubility of nabumetone decreased.

![Figure 1: Structure of Nabumetone](https://example.com/structure.png)

**Figure 1:** Structure of Nabumetone

The solid line (——) represents highest mole fraction solubility ($X_2=6.12E-03$) when $\delta_1$=11.354 (Cal/cm$^3$)$^{0.5}$ by molar volume method and Key (●●●) represents experimental solubilities by dioxane-water binary solvent system.

When $\Delta \delta$ ($\delta_1-\delta_2$) was plotted against mole fraction solubility ($X_2$) (fig. 3), the solubility parameter of nabumetone was confirmed at 11.354 (Cal/cm$^3$)$^{0.5}$ as it is that value of $\delta_1$ at which nabumetone exhibited peak mole fraction solubility and $\Delta \delta=0$. $\delta_2$ determined by the Fedor's group substitution method was found to be 10.1689 (Cal/cm$^3$)$^{0.5}$, which is still comparable to the value obtained by solubility measurement method and molar volume method.

**Figure 3:** Mole fraction solubility versus ($\delta_1-\delta_2$) profile of nabumetone

Curve showing mole fraction solubility of nabumetone ($X_2$) versus difference between solubility parameter of solvent and solute ($\delta_1-\delta_2$) and when $\Delta \delta=0$, then nabumetone exhibit highest mole fraction solubility by molar volume method.

**CONCLUSION**

Therefore, experimentally determined solubility parameter of nabumetone in water-dioxane binary solvent system was in good agreement with that of the theoretically determined solubility parameter by Molar volume method and by Fedor’s group substitution method.

**ACKNOWLEDGEMENTS**

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**REFERENCES**